

3/9/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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02757060 Genuine Article#: MA816 Number of References:
28

Title: INHIBITION OF HUMAN LUNG- CANCER CELL-LINE GROWTH
BY AN

ANTI-P185(HER2) ANTIBODY

Author(s): KERN JA; TORNEY L; WEINER D; GAZDAR A; SHEPARD
HM; FENDLY B

Corporate Source: UNIV IOWA,DEPT MED,DIV PULM DIS,C-33A
GH,200 HAWKINS

DR/IOWA CITY//IA/52242; UNIV PENN,DEPT
MED/PHILADELPHIA//PA/19104; UNIV

TEXAS,HLTH SCI CTR,SW MED SCH,DEPT
PATHOL/DALLAS//TX/75235; GENENTECH

INC/S SAN FRANCISCO//CA/00000

Journal: AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR
BIOLOGY, 1993

, V9, N4 (OCT), P448-454

ISSN: 1044-1549

Language: ENGLISH Document Type: ARTICLE

Geographic Location: USA

Subfile: SciSearch; CC LIFE--Current Contents, Life
Sciences

Journal Subject Category: CYTOLOGY & HISTOLOGY;
BIOCHEMISTRY & MOLECULAR

BIOLOGY; RESPIRATORY SYSTEM

Abstract: p185HER2, the product of the c-erbB-2 or HER2
gene, is a

membrane-bound tyrosine kinase that has structural
similarity to the

epidermal growth factor receptor. Functionally,
interaction of HER2

with its ligand or p185HER2 antibodies affects the
growth and

differentiation of HER2-expressing breast cancer cell
lines. As

p185HER2 is also expressed in human lung cancers and
human lung

cancer cell lines, we hypothesized that these cell
lines would also

respond to p185HER2 antibodies. To test this
hypothesis, we cultured

human non-small cell lung cancer cell lines in the
presence of a

p185HER2 monoclonal antibody called 4D5. 4D5 inhibited the growth of p185HER2-expressing cell lines in a dose-dependent fashion. In addition, BEAS.2B, a p185HER2-nonexpressing bronchial epithelial cell line, was transfected with the HER2 cDNA, resulting in high-level p185HER2 expression, and growth of BEAS.HER2 was now inhibited by 4D5 exposure. Mechanistically, 4D5 appeared to have a weak agonist effect on the tyrosine kinase function of p185HER2, as exposure of p185HER2-expressing cell lines to 4D5 resulted in increased p185HER2 phosphorylation. Furthermore, inhibition of tyrosine kinase function with Genistein reversed the 4D5-induced growth inhibition. Therefore, 4D5 can regulate the growth of p185HER2-expressing lung cancer cell lines through agonist effects on p185HER2.

Identifiers--KeyWords Plus: TUMOR NECROSIS FACTOR; NEU ONCOGENE;

FACTOR-RECEPTOR; MONOCLONAL-ANTIBODY; POINT MUTATION; EXPRESSION; GENE;

PROTEIN; C-ERBB-2; PROTOONCOGENE
Research Fronts: 91-1779 005 (C-ERBB-2 PROTEIN EXPRESSION;

PARAFFIN-EMBEDDED INVASIVE BREAST-CANCER ; NEU ONCOGENE)

91-0307 001 (NERVE GROWTH-FACTOR RECEPTOR IMMUNOREACTIVITY;

HIGH-AFFINITY NGF BINDING REQUIRES COEXPRESSION;
CULTURED RAT EMBRYONIC
CNS CELLS)

91-0452 001 (INHIBITION OF THE EPIDERMAL GROWTH-FACTOR RECEPTOR

TYROSINE KINASE; ALPHA-SUBSTITUTED
BENZYLIDENEMALONONITRILE

TYRPHOSTINS; EARLY SEA-URCHIN EMBRYOS)
Cited References:

AKIYAMA T, 1987, V262, P5592, J BIOL CHEM
BARGMANN CI, 1986, V45, P649, CELL
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COUSSENS L, 1985, V230, P1132, SCIENCE

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 HOLMES WE, 1992, V256, P1205, SCIENCE
 HUDZIAK RM, 1989, V9, P1165, MOL CELL BIOL
 KERN JA, 1992, V6, P359, AM J RESP CELL MOL
 KERN JA, 1990, V50, P5184, CANCER RES
 NOGUCHI M, 1993, V53, P2035, CANCER
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 SARUP JC, 1991, V1, P72, GROWTH REGULAT
 SCHECHTER AL, 1984, V312, P513, NATURE
 SCHNEIDER PM, 1989, V49, P4968, CANCER RES
 SCOTT GK, 1991, V266, P4300, J BIOL CHEM
 SEMBA K, 1985, V82, P6497, P NATL ACAD SCI USA
 SHEPARD HM, 1991, V11, P117, J CLIN IMMUNOL
 SHI D, 1991, V5, P213, MOL CARCINOGEN
 STERN DF, 1988, V8, P3969, MOL CELL BIOL
 SUGARMAN BJ, 1985, V230, P943, SCIENCE
 TATEISHI M, 1991, V27, P1372, EUR J CANCER
 WEINER DB, 1990, V50, P421, CANCER RES
 WEINER DB, 1989, V339, P230, NATURE
 YAMAMOTO T, 1986, V319, P230, NATURE

3/9/2 (Item 1 from file: 94)
 DIALOG(R) File 94:JICST-EPlus
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04934460 JICST ACCESSION NUMBER: 01A0723890 FILE
 SEGMENT: JICST-E
 Treatment for Progressive Recurrent Breast Cancer by
 Combination Therapy
 of Anti- HER2 Antibody(Herceptin) and
 Paclitaxel(Taxol).
 NAKAJIMA HIROO (1); SAKAGUCHI KOICHI (1); MIZUTA NARUHIKO
 (1); SAWAI
 KIYOSHI (1)
 (1) Kyotofuidai Naibumpitsunyusengeka
 Biotherapy(Tokyo), 2001, VOL.15,NO.3, PAGE.336-339, FIG.1,
 TBL.1, REF.7
 JOURNAL NUMBER: L0028AAT ISSN NO: 0914-2223
 UNIVERSAL DECIMAL CLASSIFICATION: 615.277.3.03 615.37.03
 616-006-08:615.37
 LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
 DOCUMENT TYPE: Journal

ARTICLE TYPE: Original paper

MEDIA TYPE: Printed Publication

ABSTRACT: Background: Herceptin is a monoclonal anti-HER2/new cancer gene

protein antibody. Previous reports have shown that for progressive

recurrent breast cancer with a high level of HER2/neu expression, the

curative rate when using Herceptin together with Taxan series agents is

higher(over 60%) than treatment with Herceptin only. Based on these

reports, we treated 5 progressive recurrent cases with combination

therapy of Herceptin and Taxol. Patients and Methods: five recurrent

cases were treated(local recurrence: 2 cases; bone metastasis: 4 cases;

lungs metastasis: 2; cases brain metastasis: one case; remote lymph

node metastasis: one case, including multiple cases). In these cases,

HER2/neu expression was more than 2+ by immunohistochemical staining in

each dissected tumor have shown that. Among these 5 cases, 3 were

previously treated with CAF or CMF. At least 3 cycles of therapy were

performed. One cycle included dosages of Herceptin(110mg/body) and

Taxol(80mg/m²) every week for 4 weeks followed by an interval for two

weeks. Result: In case 1, the skin metastasis disappeared more than 90%

with the first cycle, showing a marked effect. However heart toxicity

appeared within the second period, and we discontinued this treatment.

In the other 4 cases, treatment could be continued without any defined

side effects. The curative effect from this therapy at present shows 3

cases with PR(partial response) and NC(no change) in the others. In

treating the minimal side effect from Taxol, Syakuyaku-kanzoutou was

effective for the nervous system symptoms typical of this drug.

Discussion: We are currently analyzing the mechanism of the combination

effect in vitro in detail. Upregulation of apoptosis in HER2/neu

positive cancer cells is suggested to be one of the main mechanisms.

(author abst.)

DESCRIPTORS: human(primates); case report; adult(person); woman; breast

tumor ; immunotherapy; drug therapy; combination therapy; antitumor

drug; oncoprotein; monoclonal antibody; antitumor action; recurrence;

neoplasm staging; metastasis; bone tumor ; lung tumor ; brain

tumor ; tumor antigen; repeated administration; tumor regression;

effectiveness; cytotoxicity; neurologic manifestation; side effect;

histological diagnosis; toxicity; Chinese drug; aminoalcohol;

aminocarboxylic acid; olefin compound; carboxylate(ester); hydroxy

ketone; hydroxy acid; polyol; bridged compound; oxygen heterocyclic

compound; alicyclic compound; fatty acid; secondary alcohol; aromatic

carboxylic acid

IDENTIFIERS: cardiotoxicity; Shao-Yao-Gan-Cao-Tang; scirrhous carcinoma

BROADER DESCRIPTORS: reporting; action and behavior; growth stage;

human(sociology); femininity; sex; tumor ; disease; breast disease;

therapy; drug; protein; antibody; pharmacological action; action and

effect; metabasis; tumor process; process; bone disease; bone and

joint disease; respiratory tract tumor ; respiratory tract disease;

lung disease; nervous system neoplasm; nervous system disease; brain

disease; central nervous system disease; antigen; medication method;

administration(biology); property; symptom; clinical
laboratory test;
medical examination; inspection; diagnosis; crude drug;
amine; alcohol;
hydroxy compound; carboxylic acid; ester; ketone;
carbonyl compound;
heterocyclic compound; aliphatic carboxylic acid;
aromatic compound
CLASSIFICATION CODE(S): GW16020L; GW22020O; GE03035B

9/3/8 (Item 2 from file: 6)
DIALOG(R)File 6:NTIS
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0135106 NTIS Accession Number: PB-175 577/XAB

Preparation of Antigens and Antisera for Influenza Virus Types

(Semiannual progress rept. 1 Sep 66-1 Mar 67)

Beardmore, W. B.

Parke, Davis and Co., Detroit, Mich.

Corp. Source Codes: 276400

1 Mar 67 21p

Journal Announcement: USGRDR6718

This report consists of pages 2-22. Order as PB-175 576.

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NTIS Prices: PC A02/MF A01

9/3/19 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09136772 97071273 PMID: 8914198

Formulation development of an antifibrin monoclonal antibody radiopharmaceutical.

Kamat MS; Tolman GL; Brown JM

Centocor Inc., Malvern, Pennsylvania 19355, USA.

Pharmaceutical biotechnology (UNITED STATES) 1996 , 9 p343-64,

ISSN 1078-0467 Journal Code: BYR

Languages: ENGLISH

Document type: Journal Article; Review; Review, Tutorial

Record type: Complete 17/3/1 (Item 1 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

13232322 BIOSIS NO.: 200100439471

Protein formulation.

AUTHOR: Andya James(a); Cleland Jeffrey L; Hsu Chung C; Lam Xanthe M;

Overcashier David E; Shire Steven J; Yang Janet Yu-Feng; Wu Sylvia

Sau-Yan

AUTHOR ADDRESS: (a)Millbrae, CA**USA

JOURNAL: Official Gazette of the United States Patent and Trademark Office
Patents 1248 (5):pNo Pagination July 31, 2001

MEDIUM: e-file

ISSN: 0098-1133

DOCUMENT TYPE: Patent

RECORD TYPE: Abstract

LANGUAGE: English

17/3/2 (Item 2 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

13157206 BIOSIS NO.: 200100364355

Modulation of antigenicity related to changes in antibody flexibility upon lyophilization.

AUTHOR: Taschner Nicole; Muller Shirley A; Alumella Venkateshwar R; Goldie

Kenneth N; Drake Alex F; Aebi Ueli; Arvinte Tudor(a)

AUTHOR ADDRESS: (a)Biotechnology Development and Production, Novartis

Pharma AG, CH-4002, Basel: tudor.arvinte@pharma.novartis.com**Switzerland

JOURNAL: Journal of Molecular Biology 310 (1):p169-179 29 June, 2001

MEDIUM: print

ISSN: 0022-2836

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

17/3/14 (Item 14 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

10793300 BIOSIS NO.: 199799414445

Stability assessment of lyophilized intravenous immunoglobulin after reconstitution in glass containers and poly(vinyl chloride) bags.

AUTHOR: Parti Rajesh(a); Mankarious Samia

AUTHOR ADDRESS: (a)Stability Assurance, Baxter Healthcare Corp., Hyland Div., 1710 Flower Ave., Duarte, CA 91010**USA

JOURNAL: Biotechnology and Applied Biochemistry 25 (1):p13-18 1997

ISSN: 0885-4513

RECORD TYPE: Abstract

LANGUAGE: English

17/3/16 (Item 16 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

10354462 BIOSIS NO.: 199698809380

Development of stable lyophilized monoclonal antibody formulations:

Effect of excipients on stability.

AUTHOR: Bam Narendra; Dal Monte Paul R; Duddu Sarma P

AUTHOR ADDRESS: Pharm. Dev., SmithKline Beecham Pharm., King of Prussia, PA 19406**USA

JOURNAL: Abstracts of Papers American Chemical Society 211 (1-2):pBIOT 143 1996

CONFERENCE/MEETING: 211th American Chemical Society National Meeting New Orleans, Louisiana, USA March 24-28, 1996

ISSN: 0065-7727

RECORD TYPE: Citation

LANGUAGE: English

17/3/17 (Item 17 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

10143673 BIOSIS NO.: 199698598591

Degradation of lyophilized and reconstituted MACROSCINT (DTPA-IgG):

Precipitation vs glucosylation.

AUTHOR: Hekman Carla(a); Park Sungae; Teng Wen-Yu; Guzman Norberto A; Rossi Thomas

AUTHOR ADDRESS: (a)Analytical Res. Dev., R. W. Johnson Pharmaceutical Res. Inst., 1000 Route 202, Raritan, NJ 08869**USA

JOURNAL: Journal of Pharmaceutical and Biomedical Analysis 13 (10):p 1249-1261 1995

ISSN: 0731-7085

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

17/3/18 (Item 18 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

10085376 BIOSIS NO.: 199598540294

Safety and immunogenicity of liquid (LIQU) combination of DTP-PRPT vs. a lyophilized (LYOPH) PRPT reconstituted with DTP.

AUTHOR: Amir J(a); Dagan R; Ethevenaux C; Fritzell B

AUTHOR ADDRESS: (a)Tel-Aviv Univ., Tel-Aviv**Israel

JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 35 (0):p170 1995

CONFERENCE/MEETING: 35th Interscience Conference on Antimicrobial Agents and Chemotherapy San Francisco, California, USA September 17-20, 1995

RECORD TYPE: Citation

LANGUAGE: English

17/3/24 (Item 24 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

08070649 BIOSIS NO.: 000093092097

THE INFLUENCE OF SUCROSE DEXTRAN AND HYDROXYPROPYL-BETA-CYCLODEXTRIN AS LYOPROTECTANTS FOR A FREEZE-DRIED MOUSE IGG-2A MONOCLONAL ANTIBODY MN12

AUTHOR: RESSING M E; JISKOOT W; TALSMAN H; VAN INGEN C W; BEUVERY E C; CROMMELIN D J A

AUTHOR ADDRESS: DEP. PHARMACEUTICS, FAC. PHARM., UNIV. UTRECHT, BOX 80082, 3508 TB UTRECHT, NETH.

JOURNAL: PHARM RES (N Y) 9 (2). 1992. 266-270. 1992

FULL JOURNAL NAME: Pharmaceutical Research (New York)

CODEN: PHREE

RECORD TYPE: Abstract

LANGUAGE: ENGLISH 17/3/33 (Item 33 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

(c) 2001 BIOSIS. All rts. reserv.

03277024 BIOSIS NO.: 000072005127

LYOPHILIZED HYPER IMMUNE EQUINE SERUM AS A SOURCE OF ANTIBODIES FOR NEONATAL FOALS

AUTHOR: BURTON C; HINTZ H F; KEMEN M J; HOLMES D F

AUTHOR ADDRESS: DEP. CLIN. SCI., COLL. VET. MED., CORNELL UNIV., ITHACA, NY 14853.

JOURNAL: AM J VET RES 42 (2). 1981. 308-310. 1981

FULL JOURNAL NAME: American Journal of Veterinary Research

CODEN: AJVRA

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

17/3/41 (Item 4 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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09465010 Genuine Article#: 408VL No. References: 34

Title: A specific molar ratio of stabilizer to protein is required for storage stability of a lyophilized monoclonal antibody

Author(s): Cleland JL (REPRINT) ; Lam X; Kendrick B; Yang J; Yang TH; Overcashier D; Brooks D; Hsu C; Carpenter JF

Corporate Source: Genentech Inc, Pharmaceut R&D, 1 DNA Way/S San Francisco//CA/94070 (REPRINT); Genentech Inc, Pharmaceut R&D, S San Francisco//CA/94070; Amgen Inc, Dept Pharmaceut, Thousand Oaks//CA/91320; Genentech Inc, Qual Control, S San Francisco//CA/94070; Univ Colorado, Hlth Sci Ctr, Dept Pharmaceut Sci, Denver//CO/

Journal: JOURNAL OF PHARMACEUTICAL SCIENCES, 2001, V90, N3 (MAR), P310-321

ISSN: 0022-3549 Publication date: 20010300

Publisher: JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA

Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

17/3/53 (Item 16 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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01199018 Genuine Article#: GD532 No. References: 10

Title: STABLE LYOPHILIZED REAGENTS FOR THE SERUM FERRITIN ASSAY

Author(s): WORWOOD M; THORPE SJ; HEATH A; FLOWERS CH; COOK JD

Corporate Source: UNIV WALES COLL MED, DEPT HAEMATOL/CARDIFF CF4 4XN/S GLAM/WALES/; NATL INST BIOL STAND & CONTROLS/S MIMMS EN6

3QG/HERTS/ENGLAND/; UNIV KANSAS, MED CTR, DEPT INTERNAL MED, HAEMATOL SECT/KANSAS CITY//KS/66103

Journal: CLINICAL AND LABORATORY HAEMATOLOGY, 1991, V13, N3, P297-305

Language: ENGLISH Document Type: ARTICLE (Abstract Available)

17/3/73 (Item 2 from file: 144)

DIALOG(R)File 144:Pascal

(c) 2001 INIST/CNRS. All rts. reserv.

12895576 PASCAL No.: 97-0160846

Stability assessment of lyophilized intravenous immunoglobulin after reconstitution in glass containers and poly(vinyl chloride) bags.

Commentary

SAPAN C V comment; PARTI R; MANKARIOUS S

NABI (R) , P.O. Box 310701, Boca Raton, FL 33431-0701, United States;
Stability Assurance, Baxter Healthcare Corporation, Hyland Division, 1710
Flower Avenue, Duarte, CA 91010, United States; Biopharmaceutics, Baxter
Healthcare Corporation, Hyland Division, 1710 Flower Avenue, Duarte, CA
91010, United States

Journal: Biotechnology and applied biochemistry, 1997, 25 (1) 9-11,13-18
(9 p.)

Language: English

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17/3/75 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09318319 97218594 PMID: 9066031

Immunogenicity and safety of a liquid combination of DTP-PRP-T
[corrected] vs lyophilized PRP-T reconstituted with DTP.

Amir J; Melamed R; Bader J; Ethevenaux C; Fritzell B; Cartier JR;
Arminjon F; Dagan R

Department of Pediatrics C, Schneider Children's Medical Center of
Israel, Petah Tiqva, Israel.

Vaccine (ENGLAND) Feb 1997, 15 (2) p149-54, ISSN 0264-410X

Journal Code: X60

Erratum in Vaccine 1997 Nov;15(16) 1813

Languages: ENGLISH

Document type: Clinical Trial; Journal Article; Multicenter Study;
Randomized Controlled Trial

Record type: Completed

17/3/78 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

04728023 81253873 PMID: 6266291

Lyophilized hyperimmune equine serum as a source of antibodies for
neonatal foals.

Burton SC; Hintz HF; Kemen MJ; Holmes DF

American journal of veterinary research (UNITED STATES) Feb 1981, 42
(2) p308-10, ISSN 0002-9645 Journal Code: 40C

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

27433 LYOPHILIZ?
 333309 BULK?
 3763387 AGENT?
 1389 BULK?(W)AGENT?
 493249 CARRIER
 128806 CARRY
 2499525 ANTIBOD?
 S1 60 LYOPHILIZ? AND (BULK?(W)AGENT? OR CARRIER OR CARRY) AND
 ANTIBOD?
 ?s her2(s)antibod?
 4806 HER2
 2499525 ANTIBOD?
 S2 1440 HER2(S)ANTIBOD?
 ?s treat?(w)(cancer? or neoplas? or malignat?)
 Processing
 Processed 10 of 12 files ...
 Completed processing all files
 8793864 TREAT?
 2524718 CANCER?
 1980117 NEOPLAS?
 168 MALIGNAT?
 S3 8848 TREAT?(W) (CANCER? OR NEOPLAS? OR MALIGNAT?)
 ?s s1 and s2 and s3
 60 S1
 1440 S2
 8848 S3
 S4 0 S1 AND S2 AND S3
 ?s s1 and s2
 60 S1
 1440 S2
 S5 5 S1 AND S2
 ?t /full/all

5/9/1 (Item 1 from file: 5)
 DIALOG(R)File 5:Biosis Previews(R)
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12107717 BIOSIS NO.: 199900402566

Lyophilization of protein formulations in vials: Investigation of the
 relationship between resistance to vapor flow during primary drying and
 small-scale product collapse.

AUTHOR: Overcashier David E(a); Patapoff Thomas W; Hsu Chung C
 AUTHOR ADDRESS: (a)Department of Pharmaceutical Research and Development,
 Genentech, Inc., 1 DNA Way, South San Fra**USA

JOURNAL: Journal of Pharmaceutical Sciences 88 (7):p688-695 July, 1999

ISSN: 0022-3549

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: During the **lyophilization** process, formulations containing
 protein, **bulking agent**, or lyoprotectant form a dry product layer
 that can affect the transport of sublimed water vapor. We carried out an
 investigation of the primary drying segment of **lyophilization** to
 evaluate the relationship between the resistance to water vapor flow
 through the dried layer and the microstructure of the dried cake.
 Recombinant humanized **antibody HER2** (rhuMAb **HER2**) formulated in
 trehalose was studied, as were protein-free formulations containing
 trehalose and sucrose. Sublimation rate and product temperature data were
 used to compute the resistance to mass transfer. Dried cake structure was
 examined by scanning electron microscopy and a novel fluorescence
 microscopy method. Collapse temperatures were determined by freeze-drying
 microscopy. Mass transfer resistance was found to decrease with increases
 in temperature for each material. Resistance also depended on
 composition, decreasing in the formulation series, rhuMAb **HER2**,
 trehalose, sucrose. The **lyophilized** material consisted of porous cakes,
 with a distinct denser region at the top. Formulation and temperature

affected the microstructure of the dried cakes. The formulated trehalose and sucrose were seen, by both microscopy techniques, to possess small (2-20 μm) holes in their platelike structures after **lyophilization**. The quantity of holes was higher for material dried at higher temperature. The collapse temperature (T_c) of a material appeared to play a role in the process, as lower T_c was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

REGISTRY NUMBERS: 57-50-1: SUCROSE; 99-20-7: TREHALOSE

DESCRIPTORS:

MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Methods and Techniques; Pharmacology

CHEMICALS & BIOCHEMICALS: protein--pharmaceutical formulations; recombinant humanized **antibody HER2**; sucrose; trehalose

METHODS & EQUIPMENT: fluorescence microscopy--analytical method; freeze-drying microscopy--analytical method; **lyophilization**--biochemical method; scanning electron microscopy--analytical method

MISCELLANEOUS TERMS: water vapor flow

CONCEPT CODES:

22002 Pharmacology-General

10050 Biochemical Methods-General

10060 Biochemical Studies-General

23001 Temperature: Its Measurement, Effects and Regulation-General
Measurement and Methods

10502 Biophysics-General Biophysical Studies

5/9/2 (Item 1 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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07841406 Genuine Article#: 214HP Number of References: 20

Title: Lyophilization of protein formulations in vials: Investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse

Author(s): Overcashier DE (REPRINT); Patapoff TW; Hsu CC

Corporate Source: GENENTECH INC, DEPT PHARMACEUT RES & DEV, 1 DNA WAY/S SAN FRANCISCO//CA/94080 (REPRINT)

Journal: JOURNAL OF PHARMACEUTICAL SCIENCES, 1999, V88, N7 (JUL), P688-695

ISSN: 0022-3549 Publication date: 19990700

Publisher: AMER PHARMACEUTICAL ASSN, 2215 CONSTITUTION AVE NW, WASHINGTON, DC 20037

Language: English Document Type: ARTICLE

Geographic Location: USA

Subfile: CC LIFE--Current Contents, Life Sciences

Journal Subject Category: CHEMISTRY, MEDICINAL; PHARMACOLOGY & PHARMACY; CHEMISTRY

Abstract: During the **lyophilization** process, formulations containing protein, **bulking agent**, or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of **lyophilization** to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized **antibody HER2** (rhuMab **HER2**) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMab **HER2**, trehalose, sucrose. The **lyophilized** material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature affected the microstructure of the dried cakes. The formulated trehalose and sucrose were seen, by both microscopy

techniques, to possess small (2-20 μ m) holes in their platelike structures after **lyophilization**. The quantity of holes was higher for material dried at higher temperature. The collapse temperature (T-c) of a material appeared to play a role in the process, as lower T-c was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

Identifiers--KeyWord Plus(R): TEMPERATURE; MOISTURE; STAGE

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PRESTRELSKI SJ, 1995, V12, P1250, PHARMACEUT RES
ROY ML, 1989, V43, P60, J PARENT SCI TECHN
TOWNSEND MW, 1988, V42, P190, J PARENTER SCI TECHN

5/9/3 (Item 1 from file: 73)

DIALOG(R)File 73:EMBASE

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07761547 EMBASE No: 1999244329

Lyophilization of protein formulations in vials: Investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse

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Journal of Pharmaceutical Sciences (J. PHARM. SCI.) (United States)
1999, 88/7 (688-695)

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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 20

During the **lyophilization** process, formulations containing protein, **bulking agent**, or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of **lyophilization** to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized **antibody HER2** (rhuMab **HER2**) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMab **HER2**, trehalose, sucrose. The **lyophilized** material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature affected the microstructure of the dried cakes. The formulated trehalose

and sucrose were seen, by both microscopy techniques, to possess small (2-20 μm) holes in their platelike structures after **lyophilization**. The quantity of holes was higher for material dried at higher temperature. The collapse temperature ($T(c)$) of a material appeared to play a role in the process, as lower $T(c)$ was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

MEDICAL DESCRIPTORS:

*freeze drying; *drug formulation
water vapor; scanning electron microscopy; fluorescence microscopy;
temperature; article

SECTION HEADINGS:

039 Pharmacy

5/9/4 (Item 1 from file: 144)

DIALOG(R) File 144:Pascal

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14180821 PASCAL No.: 99-0379550

Lyophilization of protein formulations in vials : Investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse

OVERCASHIER D E; PATAPOFF T W; HSU C C

Department of Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States

Journal: Journal of pharmaceutical sciences, 1999, 88 (7) 688-695

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Document Type: P (Serial) ; A (Analytic)

Country of Publication: United States

Language: English

square During the **lyophilization** process, formulations containing protein, **bulking agent**, or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of **lyophilization** to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized **antibody HER2** (rhuMab **HER2**) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMab **HER2**, trehalose, sucrose. The **lyophilized** material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature affected the microstructure of the dried cakes. The formulated trehalose and sucrose were seen, by both microscopy techniques, to possess small (2-20 μm) holes in their platelike structures after **lyophilization**. The quantity of holes was higher for material dried at higher temperature. The collapse temperature ($T_{SUB\ c}$) of a material appeared to play a role in the process, as lower $T_{SUB\ c}$ was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of **lyophilization** may be due to small-scale product collapse.

English Descriptors: Freeze drying; Dosage form; Pharmaceutical technology; **Antibody**; Recombinant protein; Trehalose; Histidine; Polysorbate; Human; Resistance; Mass transfer; Sublimation

French Descriptors: Lyophilisation; Forme pharmaceutique; Technologie pharmaceutique; Anticorps; Proteine recombinante; Trehalose; Histidine;

Polysorbate; Homme; Resistance; Transfert masse; Sublimation

Classification Codes: 002B02A03

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5/9/5 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10196849 99322067 PMID: 10393566

Lyophilization of protein formulations in vials: investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse.

Overcashier DE; Patapoff TW; Hsu CC

Department of Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, USA.

Journal of pharmaceutical sciences (UNITED STATES) Jul 1999, 88 (7) p688-95, ISSN 0022-3549 Journal Code: JO7

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Document type: Journal Article

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Subfile: INDEX MEDICUS

During the lyophilization process, formulations containing protein, bulking agent, or lyoprotectant form a dry product layer that can affect the transport of sublimed water vapor. We carried out an investigation of the primary drying segment of lyophilization to evaluate the relationship between the resistance to water vapor flow through the dried layer and the microstructure of the dried cake. Recombinant humanized antibody HER2 (rhuMab HER2) formulated in trehalose was studied, as were protein-free formulations containing trehalose and sucrose. Sublimation rate and product temperature data were used to compute the resistance to mass transfer. Dried cake structure was examined by scanning electron microscopy and a novel fluorescence microscopy method. Collapse temperatures were determined by freeze-drying microscopy. Mass transfer resistance was found to decrease with increases in temperature for each material. Resistance also depended on composition, decreasing in the formulation series, rhuMab HER2, trehalose, sucrose. The lyophilized material consisted of porous cakes, with a distinct denser region at the top. Formulation and temperature affected the microstructure of the dried cakes. The formulated trehalose and sucrose were seen, by both microscopy techniques, to possess small (2-20 microm) holes in their platelike structures after lyophilization. The quantity of holes was higher for material dried at higher temperature. The collapse temperature (Tc) of a material appeared to play a role in the process, as lower Tc was correlated with lower resistance and a greater extent of holes. Our results are consistent with the theory that lower resistance to water vapor flow in the primary drying stage of lyophilization may be due to small-scale product collapse.

Tags: Support, Non-U.S. Gov't

Descriptors: *Freeze Drying; *Proteins--chemistry--CH; Microscopy; Temperature; Volatilization

CAS Registry No.: 0 (Proteins)

Record Date Created: 19990729

?ds

Set	Items	Description
S1	60	LYOPHILIZ? AND (BULK?(W)AGENT? OR CARRIER OR CARRY) AND ANTIBOD?
S2	1440	HER2(S)ANTIBOD?
S3	8848	TREAT?(W) (CANCER? OR NEOPLAS? OR MALIGNAT?)
S4	0	S1 AND S2 AND S3
S5	5	S1 AND S2

Set	Items	Description
S1	60	LYOPHILIZ? AND (BULK?(W)AGENT? OR CARRIER OR CARRY) AND ANTIBOD?
S2	1440	HER2(S)ANTIBOD?
S3	8848	TREAT?(W) (CANCER? OR NEOPLAS? OR MALIGNAT?)
S4	0	S1 AND S2 AND S3
S5	5	S1 AND S2
S6	0	S1 AND S3
S7	47	RD S1 (unique items)
S8	64506112	PY<=1996
S9	33	S8 AND S7
S10	2251	LYOPHILIZ? AND ANTIBOD?
S11	1345	RD (unique items)
S12	1118	S11 AND S8
S13	2235029	(BULK?(W)AGENT OR CARRIER? OR CARR?)
S14	164393	RECONSTITUT?
S15	6119450	D
S16	6119450	D
S17	90	S14 AND S11

?s s2 and s3

1440 S2

8848 S3

S18 7 S2 AND S3

?rd

...completed examining records

S19 4 RD (unique items)

?t /full/all

19/9/1 (Item 1 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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09978608 Genuine Article#: 472RZ Number of References: 71

Title: Mechanism of action of anti- HER2 monoclonal antibodies

Author(s): Baselga J. (REPRINT) ; Albanell J

Corporate Source: Hosp Gen Univ Vall Hebron, Dept Med Oncol, Med Oncol Serv, Psg Vall Hebron 119-129/Barcelona 08035//Spain/ (REPRINT); Hosp Gen Univ Vall Hebron, Dept Med Oncol, Med Oncol Serv, Barcelona 08035//Spain/

Journal: ANNALS OF ONCOLOGY, 2001, V12, 1, P35-41

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Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS

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Geographic Location: Spain

Journal Subject Category: ONCOLOGY

Abstract: The search for new methods of **treating cancer**, combined with advances in our understanding of carcinogenesis, molecular biology and technology, has resulted in the development of novel biologic agents with proven clinical efficacy. One such agent is trastuzumab (Herceptin), a humanized monoclonal **antibody** that targets the human epidermal growth factor receptor-2 (**HER2**). **HER2** is a member of a family of receptors that interact with each other and various ligands to stimulate various intracellular signal transduction pathways involved in cell growth control. **HER2** is overexpressed in 20%-30% of women with breast cancer and is associated with aggressive tumor characteristics and poor prognosis. Trastuzumab is the first humanized monoclonal **antibody** to be approved for therapeutic use and the first oncogene-targeted treatment with proven survival benefit in women with **HER2**-positive metastatic breast cancer. However, its mechanism of action has not been fully characterized and appears to be complex. This paper reviews current knowledge of the mechanism of action of trastuzumab, including **HER2** protein downregulation, prevention of **HER2**-containing heterodimer formation, initiation of G1 arrest and induction of p27, prevention of **HER2** cleavage, inhibition of angiogenesis, and induction of immune mechanisms. The significance of these mechanisms for selection of concomitant chemotherapy is also considered.

Descriptors--Author Keywords: **HER2** ; mechanism of action ; monoclonal

antibodies ; signal transduction ; Herceptin ; trastuzumab
Identifiers--Keyword Plus(R): METASTATIC BREAST-CANCER; EPIDERMAL
GROWTH-FACTOR; TUMOR-CELL-LINES; TYROSINE KINASE-ACTIVITY; CARCINOMA
CELLS; FACTOR RECEPTOR; EXTRACELLULAR DOMAIN; C-ERBB-2 ONCOPROTEIN;
NECROSIS FACTOR; ERBB RECEPTORS

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YU DH, 1998, V2, P581, MOL CELL

19/9/2 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection
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02396129 4563089

Antibody-induced apoptosis

Arakawa, T.; Kita, Y.

Amgen Inc.

PATENT NUMBER: US 5783186

(1998)

DOCUMENT TYPE: Patent LANGUAGE: ENGLISH

SUBFILE: Medical and Pharmaceutical Biotechnology Abstracts

Anti-Her2 antibodies which induce apoptosis in Her2 expressing cells are disclosed. The antibodies are used to "tag" Her2 overexpressing tumors for elimination by the host immune system. Also disclosed are hybridoma cell lines producing the antibodies, methods for treating cancer using the antibodies, and pharmaceutical compositions.

DESCRIPTORS: Patents; Apoptosis; Monoclonal antibodies; Hybridoma; Tumors;
HER2 protein

SECTION HEADING: 33050 -- Patents; 33375 -- Antibodies

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DIALOG(R)File 399:CA SEARCH(R)
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135288636 CA: 135(20)288636p PATENT

Synergistic methods and compositions for treating cancer using two or more anticancer agents

INVENTOR(AUTHOR): Lee, Francis Y.

LOCATION: USA

ASSIGNEE: Bristol-Myers Squibb Company

PATENT: PCT International ; WO 200172721 A2 DATE: 20011004

APPLICATION: WO 2001US9193 (20010322) *US PV192278 (20000327)

PAGES: 81 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C07D-243/00A

DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

SECTION:

CA226006 Biomolecules and Their Synthetic Analogs

CA201XXX Pharmacology

CA228XXX Heterocyclic Compounds (More Than One Hetero Atom)

CA230XXX Terpenes and Terpenoids

CA263XXX Pharmaceuticals

IDENTIFIERS: imidazolybenzodiazepine anticancer synergistic treatment
cancer, chemotherapy synergism epothilone baccatin imidazolybenzodiazepine

DESCRIPTORS:

Antibodies...

anti-Her2 and imclone antibody C225; synergistic methods using two or more anticancer agents for treating cancer

Enzymes,biological studies...
 antineoplastic; synergistic methods using two or more anticancer agents
 for treating cancer

Intestine,neoplasm...
 colon, carcinoma, inhibitors; synergistic methods using two or more
 anticancer agents for treating cancer

Antitumor agents...
 colon carcinoma; synergistic methods using two or more anticancer
 agents for treating cancer

Intestine,neoplasm...
 colon, inhibitors; synergistic methods using two or more anticancer
 agents to kill a colon cancer xenograft

Antitumor agents...
 colon; synergistic methods using two or more anticancer agents to kill
 a colon cancer xenograft

Chemotherapy...
 combination; synergistic methods using two or more anticancer agents
 for treating cancer

Nucleosides,biological studies...
 cytotoxic; synergistic methods using two or more anticancer agents for
 treating cancer

Anthracyclines...
 drug; synergistic methods using two or more anticancer agents for
 treating cancer

Platelet-derived growth factors...
 inhibitors; synergistic methods using two or more anticancer agents for
 treating cancer

Drug delivery systems...
 injections; synergistic methods using two or more anticancer agents for
 treating cancer

Antitumor agents...
 mammary gland; synergistic methods using two or more anticancer agents
 for treating cancer

Stabilizing agents...
 microtubule; synergistic methods using two or more anticancer agents
 for treating cancer

Mammary gland... Prostate gland...
 neoplasm, inhibitors; synergistic methods using two or more anticancer
 agents for treating cancer

Coordination compounds...
 platinum; synergistic methods using two or more anticancer agents for
 treating cancer

Antitumor agents...
 prostate gland; synergistic methods using two or more anticancer agents
 for treating cancer

Antitumor agents...
 squamous cell carcinoma; synergistic methods using two or more
 anticancer agents for treating cancer

Cooperative phenomena...
 synergism; synergistic methods using two or more anticancer agents for
 treating cancer

Alkylating agents,biological... Antitumor agents...
 Hormones,animal,biological studies... Interferons... Interleukins...

Radiotherapy... Taxanes...
 synergistic methods using two or more anticancer agents for treating
 cancer

Steroids,biological studies...
 synthetic analog; synergistic methods using two or more anticancer
 agents for treating cancer

Alkaloids,biological studies...
 vinca, drug; synergistic methods using two or more anticancer agents
 for treating cancer

CAS REGISTRY NUMBERS:
 66-22-8 biological studies, synergistic methods using two or more
 anticancer agents for treating cancer
 12794-10-4DP derivs., synergistic methods using imidazolylbenzodiazepine
 and two or more anticancer agents for treating cancer
 91-18-9 drug; synergistic methods using two or more anticancer agents for

treating cancer
 9039-48-9 80449-02-1 127464-60-2 137632-03-2 141907-41-7 142243-02-5
 142805-58-1 340830-03-7 inhibitors; synergistic methods using two or
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 50-07-7 50-18-0 50-24-8 50-44-2 51-21-8 52-24-4 53-03-2 54-62-6
 56-53-1 57-22-7 57-63-6 58-05-9 58-18-4 58-22-0 59-05-2 68-96-2
 71-58-9 76-43-7 79-22-1 83-43-2 104-94-9 108-24-7 124-94-7
 125-84-8 147-94-4 148-82-3 518-28-5 521-12-0 528-74-5 569-57-3
 595-33-5 630-19-3 645-05-6 671-16-9 801-52-5 865-21-4 968-93-4
 994-30-9 1066-35-9 2410-93-7 2998-57-4 3778-73-2 4342-03-4
 4375-07-9 7689-03-4 7751-38-4 9015-68-3 10540-29-1 11056-06-7
 13311-84-7 15228-71-4 15663-27-1 17902-23-7 19810-31-2 20830-81-3
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 65271-80-9 65807-02-5 82855-09-2 89778-26-7 90357-06-5 95058-81-4
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 335664-79-4 345627-80-7 345627-82-9 355113-84-7P 355113-86-9P
 355113-87-0P 355113-88-1P 355113-98-3P 364357-69-7 364357-70-0
 364357-72-2 364357-73-3 364357-75-5P 364357-77-7P 364357-78-8P
 364357-79-9 364357-80-2 364357-82-4 364357-83-5 synergistic methods
 using two or more anticancer agents for treating cancer

19/9/4 (Item 2 from file: 399)
 DIALOG(R) File 399:CA SEARCH(R)
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130336963 CA: 130(25)336963p PATENT
Methods and compositions comprising glycoprotein glycoforms
 INVENTOR(AUTHOR): Raju, T. Shantha
 LOCATION: USA
 ASSIGNEE: Genentech, Inc.
 PATENT: PCT International ; WO 9922764 A1 DATE: 19990514
 APPLICATION: WO 98US21925 (19981016) *US 962497 (19971031)
 PAGES: 52 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A;
 C07K-016/00B; C12P-021/00B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA;
 BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM;
 HR; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD;
 MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM;
 TR; TT; UA; UG; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
 DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY;
 DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI;
 CM; GA; GN; GW; ML; MR; NE; SN; TD; TG
 SECTION:
 CA215003 Immunochemistry
 IDENTIFIERS: glycoprotein antibody IgG immunoadhesin cancer therapy
 DESCRIPTORS:
 Tumor necrosis factors...
 chimeric; prepn. of compns. contg. glycoprotein glycoforms or
 anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins
 for treating cancer.
 Fusion proteins(chimeric proteins)...
 glyco-; prepn. of compns. contg. glycoprotein glycoforms or anti-CD20,
 HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for
 treating cancer.
 Immunoglobulins...
 immunoadhesins; prepn. of compns. contg. glycoprotein glycoforms or
 anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins
 for treating cancer.
 Antibodies... Antitumor agents... Buffers... CD20(antigen)... Containers...
 Glycoproteins(general),biological studies... IgE... IgG1... IgG... Labels
 ... Monoclonal antibodies... neu(receptor)... Salts,biological studies...

prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.

CAS REGISTRY NUMBERS:

59-23-4 biological studies, activated; prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.
7439-96-5 7440-39-3 7440-70-2 biological studies, prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.
2956-16-3 9031-68-9 9054-94-8 127464-60-2 prepn. of compns. contg. glycoprotein glycoforms or anti-CD20, HER2, VEGF, or IgE antibodies or immunoadhesin glycoproteins for treating cancer.

20/3/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10096040 BIOSIS NO.: 199598550958
Phase I trial of 2B1, a bispecific monoclonal antibody targeting c-erbB-2 and Fc-gamma-RIII.
AUTHOR: Weiner Louis M(a); Clark Joseph I; Davey Monica; Li Wei S; De Palazzo Irma Garcia; Ring David B; Alpaugh R Katherine
AUTHOR ADDRESS: (a)Dep. Med. Oncol., Fox Chase Cancer Cent., 7701 Burholme Ave, Philadelphia, PA 19111**USA
JOURNAL: Cancer Research 55 (20):p4586-4593 1995
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

20/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

09069650 BIOSIS NO.: 199497078020
Monoclonal antibodies directed to the erbB-2 receptor inhibit in vivo tumour cell growth.
AUTHOR: Harwerth I-M; Wels W; Schlegel J; Mueller M; Hynes N E(a)
AUTHOR ADDRESS: (a)Friedrich Miescher Inst., PO Box 2543, CH-4002 Basel** Switzerland
JOURNAL: British Journal of Cancer 68 (6):p1140-1145 1993
ISSN: 0007-0920
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

20/3/17 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

01381999 Genuine Article#: GU439 No. References: 49
Title: CHARACTERIZATION OF AN ANTI-P185HER2 MONOCLONAL-ANTIBODY THAT STIMULATES RECEPTOR FUNCTION AND INHIBITS TUMOR-CELL GROWTH
Author(s): SARUP JC; JOHNSON RM; KING KL; FENDLY BM; LIPARI MT; NAPIER MA; ULLRICH A; SHEPARD HM
Corporate Source: GENENTECH INC,DEPT CELL BIOL,460 POINT SAN BRUNO BLVD/S SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT CELL BIOL,460 POINT SAN BRUNO BLVD/S SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT DEV BIOL/S SAN FRANCISCO//CA/94080; MAX PLANCK INST BIOCHEM/D-8033 MARTINSRIED//FEDREP GER/
Journal: GROWTH REGULATION, 1991 , V1, N2, P72-82
Language: ENGLISH Document Type: ARTICLE (Abstract Available) 20/3/18 (Item 1 from
DIALOG(R)File 71:ELSEVIER BIOBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

00295954 95109333
Engineering high affinity humanized anti-p185(HER2)/anti-CD3 F(ab')inf 2 for efficient lysis of p185(HER2) overexpressing tumor cells
Zhu Z.; Lewis G.D.; Carter P.
ADDRESS: P. Carter, Genentech Inc, 460 Point San Bruno Boulevard, South San Francisco, CA 94080, United States
Journal: International Journal of Cancer, 62/3 (319-324), 1995 , United States
PUBLICATION DATE: 19950000
CODEN: IJCNA
ISSN: 0020-7136
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English

CLASSIFICATION CODE AND DESCRIPTION:
87.4.3.5 - CANCER RESEARCH / **TREATMENT** / Immunotherapy / Passive
86.9.3.5 - IMMUNOLOGY AND INFECTIOUS DISEASES / TUMOUR IMMUNOLOGY / Tumour

Immunotherapy / Passive 20/3/28 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
(c) 2001 INIST/CNRS. All rts. reserv.

09834477 PASCAL No.: 92-0036806

**Monoclonal antibody therapy of human cancer : taking the HER2
protooncogene to the clinic**

MICHAEL SHEPARD H; LEWIS G D; SARUP J C; FENDLY B M; MANEVAL D; MORDENTI
J; FIGARI I; KOTTS C E; PALLADINO M A JR; ULLRICH A; SLAMON D

Genentech. Inc., dep. development biology, South San Francisco CA 94080,
USA

Journal: Journal of clinical immunology, 1991 , 11 (3) 117-127

Language: English

Processing

2889337 TISSUE
4376600 TYPE?
29828 TISSUE(W)TYPE?
4053379 ORGAN?
10741901 CELL?
4376600 TYPE?
311814 CELL?(W)TYPE?
S5 4342875 (TISSUE(W)TYPE? OR ORGAN? OR CELL?(W)TYPE?)

?ds

Set	Items	Description
S1	1425	HER2(S)EXPRESSION
S2	541	RD (unique items)
S3	41149634	PY<1996
S4	135	S2 AND S3
S5	4342875	(TISSUE(W)TYPE? OR ORGAN? OR CELL?(W)TYPE?)

?s s2 and s5

	541	S2
	4342875	S5
S6	13	S2 AND S5

6/2/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11948262 BIOSIS NO.: 199900194371
Cell type-dependent and -independent control of HER-2/neu translation.
AUTHOR: Child Stephanie J; Miller Melanie K; Geballe Adam P(a)
AUTHOR ADDRESS: (a)Divisions of Molecular Medicine and Clinical Research,
Fred Hutchinson Cancer Research Center, 1**USA
JOURNAL: International Journal of Biochemistry & Cell Biology 31 (1):p
201-213 Jan., 1999
ISSN: 1357-2725
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

6/2/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

07058184 BIOSIS NO.: 000089128288
EXPRESSION OF THE P185 ENCODED BY HER2 ONCOGENE IN NORMAL AND
TRANSFORMED HUMAN TISSUES
AUTHOR: NATALI P G; NICOTRA M R; BIGOTTI A; VENTURO I; SLAMON D J; FENDLY B
M; ULLRICH A
AUTHOR ADDRESS: DEP. IMMUNOL., REGINA ELENA CANCER INST., VIALE REGINA
ELENA 291, 000161 ROME, ITALY.
JOURNAL: INT J CANCER 45 (3). 1990. 457-461. 1990
FULL JOURNAL NAME: International Journal of Cancer
CODEN: IJCNA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

6/2/12 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2001 Elsevier Science B.V. All rts. reserv.

04338038 EMBASE No: 1990226101
Expression of the HER-2/neu proto-oncogene in normal human adult and
fetal tissues
Press M.F.; Cordon-Cardo C.; Slamon D.J.
Department of Pathology, University of Southern, California, 2011 Zonal
Avenue, Los Angeles, CA 90033 United States
Oncogene (ONCOGENE) (United Kingdom) 1990, 5/7 (953-962)
CODEN: ONCNE ISSN: 0950-9232
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

et	Items	Description
S1	47	MONOCLONAL(W)ANTIBOD? AND FORMULATION AND IN(W)VIVO AND AD-MINISTRATION
S2	37	RD (unique items)
S3	334	(LYOPHILIZE? OR FREEZE(W)DRID OR FREEZE(W)DRY) AND MONOCLO-NAL(W)ANTIBOD?
S4	161	RD (unique items)
S5	23423699	IN(W)VIVO OR HUMAN?

?s s4 and s5

161 S4
23423699 S5
S6 100 S4 AND S5
7/3/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10684812 BIOSIS NO.: 199799305957

The effect of sugars and buffer excipients on the stabilization of a lyophilized formulation for an anti-IgE humanized monoclonal antibody.

AUTHOR: Andya James; Wu Sylvia; Hsu Chung; Shire Steven J
AUTHOR ADDRESS: Pharmaceutical Research Development, Genentech Inc., South San Francisco, CA 94080**USA
JOURNAL: Pharmaceutical Research (New York) 13 (9 SUPPL.):pS78 1996
CONFERENCE/MEETING: Annual Meeting of the American Association of Pharmaceutical Scientists Seattle, Washington, USA October 27-31, 1996
ISSN: 0724-8741
RECORD TYPE: Citation
LANGUAGE: English

7/3/39 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

10114387 Genuine Article#: 484QM No. References: 30
Title: Effect of moisture on the stability of a lyophilized humanized monoclonal antibody formulation
Author(s): Breen ED (REPRINT) ; Curley JG; Overcashier DE; Hsu CC; Shire SJ
Corporate Source: Genentech Inc,Pharmaceut Res & Dev,1 DNA Way/S San Francisco//CA/94080 (REPRINT); Genentech Inc,Pharmaceut Res & Dev,S San Francisco//CA/94080
Journal: PHARMACEUTICAL RESEARCH, 2001, V18, N9 (SEP), P1345-1353
ISSN: 0724-8741 Publication date: 20010900
Publisher: KLUWER ACADEMIC/PLENUM PUBL, 233 SPRING ST, NEW YORK, NY 10013 USA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

7/3/40 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

09786691 Genuine Article#: 448JN No. References: 40
Title: Modulation of antigenicity related to changes in antibody flexibility upon lyophilization
Author(s): Taschner N; Muller SA; Alumella VR; Goldie KN; Drake AF; Aebi U; Arvinte T (REPRINT)
Corporate Source: Novartis Pharma AG,Biotechnol Dev & Prod,CH-4002 Basel//Switzerland/ (REPRINT); Novartis Pharma AG,Biotechnol Dev & Prod,CH-4002 Basel//Switzerland//; Univ Basel,Biozentrum, Inst Microscopy,CH-4056 Basel//Switzerland//; European Mol Biol Lab,D-69117 Heidelberg//Germany//; Univ London Kings Coll,Dept Pharm,London SE1 8WA//England/
Journal: JOURNAL OF MOLECULAR BIOLOGY, 2001, V310, N1 (JUN 29), P169-179
ISSN: 0022-2836 Publication date: 20010629
Publisher: ACADEMIC PRESS LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

7/3/41 (Item 3 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

09465010 Genuine Article#: 408VL No. References: 34

Title: A specific molar ratio of stabilizer to protein is required for storage stability of a lyophilized monoclonal antibody

Author(s): Cleland JL (REPRINT) ; Lam X; Kendrick B; Yang J; Yang TH; Overcashier D; Brooks D; Hsu C; Carpenter JF

Corporate Source: Genentech Inc, Pharmaceut R&D, 1 DNA Way/S San Francisco//CA/94070 (REPRINT); Genentech Inc, Pharmaceut R&D, S San Francisco//CA/94070; Amgen Inc, Dept Pharmaceut, Thousand Oaks//CA/91320; Genentech Inc, Qual Control, S San Francisco//CA/94070; Univ Colorado, Hlth Sci Ctr, Dept Pharmaceut Sci, Denver//CO/

Journal: JOURNAL OF PHARMACEUTICAL SCIENCES, 2001, V90, N3 (MAR), P310-321

ISSN: 0022-3549 Publication date: 20010300

Publisher: JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012
USA

Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

7/3/89 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10424116 20052396 PMID: 10587113

Freeze-dried formulation for direct 99mTc-labeling ior-egf/r3 MAb: additives, biodistribution, and stability.

Morales AA; Nunez-Gandolff G; Perez NP; Veliz BC; Caballero-Torres I; Duconge J; Fernandez E; Crespo FZ; Veloso A; Iznaga-Escobar N

Center of Molecular Immunology, Havana, Cuba.

Nuclear medicine and biology (ENGLAND) Aug 1999, 26 (6) p717-23,

ISSN 0969-8051 Journal Code: BOO

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

7/3/95 (Item 7 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

05277337 89306482 PMID: 2744392

Characteristics of lyophilized anti-A and anti-B monoclonal antibodies used for identification of the ABO blood group system]

Kharakteristika liofilizirovannykh anti-A i anti-B monoklonal'nykh antitel dlia opredeleniia grupp krovi sistemy ABO.

Deriugina EI; Drize NI; Lemeneva LN; Chertkov IL; Gurtovoi IM

Gematologiya i transfuziologiya (USSR) May 1989, 34 (5) p61-4,

ISSN 0234-5730 Journal Code: FK6

Languages: RUSSIAN

Document type: Journal Article

Record type: Completed

Status: Path 1 of [Dialog Information Services via Modem]

Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 31060000009999...Open

DIALOG INFORMATION SERVICES

PLEASE LOGON:

***** HHHHHHHH SSSSSSSS?

Status: Signing onto Dialog

ENTER PASSWORD:

***** HHHHHHHH SSSSSSSS? *****

Welcome to DIALOG

Status: Connected

*HER2 expression
in lung carcinoma*

Dialog level 02.08.23D

Last logoff: 28aug02 08:58:32

Logon file001 28aug02 09:44:20

File 1:ERIC 1966-2002/Aug 08

(c) format only 2002 The Dialog Corporation

Set Items Description

--- -----

Cost is in DialUnits

?b 155

28aug02 09:44:24 User233719 Session D1030.1

\$0.29 0.083 DialUnits File1

\$0.29 Estimated cost File1

\$0.01 TELNET

\$0.30 Estimated cost this search

\$0.30 Estimated total session cost 0.083 DialUnits

File 155:MEDLINE(R) 1966-2002/Aug W4

*File 155: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.

Set Items Description

--- -----

?s her2

S1 916 HER2

?s her(w)2

44235 HER

2456012 2

S2 1293 HER(W)2

?s erbb2

S3 1148 ERBB2

?s erb(w)b2

1379 ERB

16607 B2

S4 236 ERB(W)B2

?s s1 or s2 or s3 or s4

916 S1

1293 S2

1148 S3

236 S4

S5 3362 S1 OR S2 OR S3 OR S4

?s lung(w) (cancer or carcinoma)

332019 LUNG

375266 CANCER

308610 CARCINOMA

August 28, 2002

S6 38734 LUNG(W) (CANCER OR CARCINOMA)
?s s5(s)s6

3362 S5

38734 S6

S7 102 S5(S)S6

?s s7 not py>1995

102 S7

3090067 PY>1995

S8 28 S7 NOT PY>1995

?rd

...completed examining records

S9 28 RD (unique items)

?ds

Set	Items	Description
S1	916	HER2
S2	1293	HER(W) 2
S3	1148	ERBB2
S4	236	ERB(W) B2
S5	3362	S1 OR S2 OR S3 OR S4
S6	38734	LUNG(W) (CANCER OR CARCINOMA)
S7	102	S5(S)S6
S8	28	S7 NOT PY>1995
S9	28	RD (unique items)

?t s9/6/1-28

9/6/1

10031516 99034861 PMID: 9816029

Localized adenocarcinoma of the lung: oncogene expression of erbB-2 and p53 in 150 patients.

Jun 1995

9/6/2

08833840 96191822 PMID: 8616111

Molecular genetic tumor markers in the early diagnosis and screening of non-small-cell lung cancer.

1995

9/6/3

08624564 95382554 PMID: 7653995

Up-regulation of urokinase-type plasminogen activator expression by the HER2/neu proto-oncogene.

Jul-Aug 1995

9/6/4

08583512 95340299 PMID: 7615356

Association between RB-1 gene alterations and factors of favourable prognosis in human breast cancer, without effect on survival.

Apr 21 1995

9/6/5

08541195 95300268 PMID: 7781111

[Gene expression of growth factors, growth factor receptor and oncogenes in human lung cancer cell lines]

Feb 1995

9/6/6

08513517 95271702 PMID: 7538595

Enhanced chemoresistance by elevation of p185neu levels in HER - 2 /neu-transfected human lung cancer cells.

May 3 1995

9/6/7

08385615 95150499 PMID: 7847823

Establishment and characterization of five human small cell lung cancer cell lines from early tumor xenografts.

Sep-Oct 1994

9/6/8

08364668 95103532 PMID: 7805040

A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation, histopathology, and oncoprotein expression.

Jan 1 1995

9/6/9

08313537 95070178 PMID: 7979412

[Advances in pathobiological research on lung carcinoma]

Nov 1994

9/6/10

08293057 95051086 PMID: 7962174

Colocalization of the p185HER2 oncoprotein and integrin alpha 6 beta 4 in Calu-3 lung carcinoma cells.

Aug 1994

9/6/11

08147112 94282743 PMID: 7912166

HER2 /neu-derived peptides are shared antigens among human non-small cell lung cancer and ovarian cancer.

Jul 1 1994

9/6/12

08117836 94243246 PMID: 8186664

Oncogene overexpression in non-small-cell lung cancer tissue: prevalence and clinicopathological significance.

Jan 1994

9/6/13

08096855 94219837 PMID: 8166465

The molecular and cellular basis of human lung cancer.

Jan-Feb 1994

9/6/14

08090616 94231684 PMID: 8176843

[Molecular diagnosis of lung carcinoma]

Apr 1994

9/6/15

07879702 94017835 PMID: 8412200

Genetic changes in lung cancer.

1993

9/6/16

07864937 94001483 PMID: 8398710

Expression of topoisomerase II alpha and beta in an adenocarcinoma cell line carrying amplified topoisomerase II alpha and retinoic acid receptor alpha genes.

Oct 1993

9/6/17

07864374 94000870 PMID: 8104437

Inhibition of human lung cancer cell line growth by an anti-p185HER2 antibody.

Oct 1993

9/6/18

07734415 93260725 PMID: 8098377

Correlation of intrinsic chemoresistance of non-small-cell lung cancer cell lines with HER - 2 /neu gene expression but not with ras gene mutations.

Jun 2 1993

9/6/19

07712015 93242881 PMID: 1300765

[The search for amplification of the ERBB-2 oncogene in human tumors]

Poisk amplifikatsii onkogena ERBB-2 v opukholiakh cheloveka.

1992

9/6/20

07659053 93177677 PMID: 7679945

Immunocytological detection of bone marrow micrometastasis in operable non-small cell lung cancer.

Mar 1 1993

9/6/21

07548209 93074378 PMID: 1444790

Molecular surgery for cancer.

Nov 1992

9/6/22

07497815 93001780 PMID: 1327031

Molecular approaches to prevention and therapy of aerodigestive tract cancers.

1992

9/6/23

07289168 92223017 PMID: 1373318

Amplification of the topoisomerase II alpha gene in a non-small cell lung cancer cell line and characterisation of polymorphisms at the human topoisomerase II alpha and beta loci in normal tissue.

Mar 1992

9/6/24

07273548 92198667 PMID: 1312850

Mechanisms of p185HER2 expression in human non-small cell lung cancer cell lines.

Apr 1992

9/6/25

07055685 91365853 PMID: 1679763

Monoclonal antibody therapy of human cancer: taking the HER2 protooncogene to the clinic.

May 1991

9/6/26

06803503 91105667 PMID: 1670993

Cytogenetic abnormalities and overexpression of receptors for growth factors in normal bronchial epithelium and tumor samples of lung cancer patients.

Jan 1 1991

9/6/27

06638920 90335831 PMID: 1974168

p185neu expression in human lung adenocarcinomas predicts shortened survival.

Aug 15 1990

9/6/28

06360408 90058477 PMID: 2573414

Amplification of protooncogenes in surgical specimens of human lung carcinomas.

Dec 1 1989

?t s9/3,ab/1,2,8,11,12,13

9/3,AB/1

DIALOG(R) File 155:MEDLINE(R)

10031516 99034861 PMID: 9816029

Localized adenocarcinoma of the lung: oncogene expression of erbB-2 and p53 in 150 patients.

Harpole D H; Marks J R; Richards W G; Herndon J E; Sugarbaker D J
Lung Cancer Research Laboratory, Division of Thoracic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

Clinical cancer research : an official journal of the American Association for Cancer Research (UNITED STATES) Jun 1995, 1 (6)
p659-64, ISSN 1078-0432 Journal Code: 9502500

Contract/Grant No.: CA56749; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Historical information and pathological material from 150 consecutive patients with localized adenocarcinoma of the lung was collected to evaluate oncogene expression of erbB-2 and p53, and erbB-2 gene amplification. Pathological material after resection was reviewed to verify histological staging, and patient follow-up was complete in all cases for at least 68 months. Immunohistochemistry of erbB-2 (HER-2/neu) and p53 oncogene expression was performed on two separate paraffin tumor blocks for each patient with normal lung as control. Gene amplification of erbB-2 was measured after DNA extraction from 20-micrometer sections of erbB-2-positive and -negative tumors. All analyses were blinded and included Kaplan-Meier survival estimates with Cox proportional hazards regression modeling. Two adequate blocks of tumor and normal lung were available for 138 (92%) patients. Immunohistochemical identification of expression of p53 was observed in 49 (37%) patients and erbB-2 in 17 (13%) patients. DNA dot blot analyses were performed on 17 erbB-2-positive and 13 randomly selected erbB-2-negative tumors. There was 1 (6%) of 17 erbB-2-positive tumors with 4-fold erbB-2 gene amplification. Actual 5-year survival was 63% and actuarial 10-year survival was 59% for the entire population of 150 patients. Significant univariate predictors ($P < 0.05$) of cancer death were the presence of symptoms, tumor size >3 cm, poor differentiation, visceral pleural invasion, and p53 expression. Multivariate analysis associated symptoms and p53 expression as independent factors with decreased survival. Thus, this project examined p53 and erbB-2 expression in patients with localized adenocarcinoma and associated p53 status with survival. Multicenter collection of data should allow the

development of a model of cancer recurrence in this most common **lung cancer**.

9/3,AB/2

DIALOG(R) File 155:MEDLINE(R)

08833840 96191822 PMID: 8616111

Molecular genetic tumor markers in the early diagnosis and screening of non-small-cell lung cancer.

Jacobson D R; Fishman C L; Mills N E

Department of Medicine, Kaplan Cancer Center, New York University Medical Center, New York, USA.

Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (NETHERLANDS) 1995, 6 Suppl 3 pS3-8, ISSN 0923-7534

Journal Code: 9007735

Contract/Grant No.: K12 CA01713-02; CA; NCI; T32 ES07267-02; ES; NIEHS

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: Little progress has been made in decreasing **lung cancer** mortality by applying conventional methods to early diagnosis and screening. Recent advances in molecular oncology, however, have provided tools which may be of use in this area. Many genes involved in controlling cell growth and differentiation are abnormal in **lung cancer** cells. Such genes include K-ras, p53, rb, myc, **her2** /neu, and probably one or more tumor suppressor genes on chromosome 3p. The involvement of these genes in **lung cancer** is reviewed. The K-ras oncogene contains a mutation in codon 12 in many cases of non-small-cell **lung cancer**, particularly adenocarcinoma, and is thus a potentially useful **lung cancer** tumor marker. **DESIGN:** We have developed a highly sensitive, simple assay for ras mutations, and applied it to bronchoalveolar lavage fluid obtained from patients undergoing evaluation for suspected **lung cancer**. **RESULTS:** In many cases, the ras assay was more sensitive than routine cytology and histopathology, demonstrating that this is a potentially clinically useful assay. **CONCLUSION:** Molecular genetic tumor markers, including mutations in ras and other genes, and/or immunohistochemical tumor markers, may provide tools which can be applied to bronchoalveolar lavage fluid or sputum, for use in diagnostic tests and in screening programs. The use of such markers may lead to decreased **lung cancer** mortality.

9/3,AB/8

DIALOG(R) File 155:MEDLINE(R)

08364668 95103532 PMID: 7805040

A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation, histopathology, and oncoprotein expression.

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Cancer research (UNITED STATES) Jan 1 1995, 55 (1) p51-6, ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: CA56749; CA; NCI

Document type: Journal Article

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In order to construct a multivariate model for predicting early recurrence and cancer death for patients with stage I non-small cell **lung cancer**, 271 consecutive patients (mean age, 63 +/- 8 years) who were diagnosed, treated, and followed at one institution were studied. All patients were clinical stage I with head and chest/abdominal computed tomograms and radionuclide bone scans without evidence of metastatic disease. Pathological material after resection was reviewed to verify

histological staging. Follow-up documented the time and location of any recurrence, was a median 56 months in duration, and was complete in all cases. Data recorded included age, sex, smoking history, presenting symptoms, pathological description, and oncoprotein staining for erbB-2 (**HER** - 2 /neu), p53, and KI-67 proliferation protein. Immunohistochemistry of oncogene expression was performed on two separate archived paraffin tumor blocks for each patient, with normal lung as control. All analyses were blinded and included Kaplan-Meier survival estimates with Cox proportional hazards regression modeling. Data, including immunohistochemistry, were complete for all 271 patients. Actual 5-year survival was 63% and actuarial 10-year survival was 58%. Significant univariate predictors ($P < 0.05$) of early recurrence and cancer-death were: male sex; the presence of symptoms; chest pain; type of cough; hemoptysis; tumor size > 3 cm diameter (T2); poor differentiation; vascular invasion; erbB-2 expression; p53 expression; and a higher KI-67 proliferation index ($> 5\%$). An additive oncogene expression curve demonstrated a 5-year survival of 72% for 136 patients without p53 or erbB-2, 58% for 108 patients who expressed either oncogene, and 38% for 27 who expressed both ($P < 0.001$). (ABSTRACT TRUNCATED AT 250 WORDS)

9/3,AB/11

DIALOG(R) File 155:MEDLINE(R)

08147112 94282743 PMID: 7912166

HER2 /neu-derived peptides are shared antigens among human non-small cell lung cancer and ovarian cancer.

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Cancer research (UNITED STATES) Jul 1 1994, 54 (13) p3387-90, ISSN 0008-5472 Journal Code: 2984705R

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Previously, we have reported a correlation between the expression of HER2/neu and sensitivity to HLA-A2-restricted cytotoxic T-cells (CTL) in ovarian cancer. To investigate the role of HER2/neu in human non-small cell **lung cancer** (NSCLC), we established autologous tumor-specific CTL from tumor-infiltrating lymphocytes of HLA-A2+ **HER2** /neu+ NSCLC patients. These CTL lines specifically recognized HLA-A2+ **HER2** /neu+ autologous and allogeneic NSCLC cell lines as well as HLA-A2+ **HER2** /neu+ heterologous ovarian cancer cell lines. Furthermore, these CTL recognized an overexpressed, **HER2** /neu-derived peptide. From these results, we conclude that HLA-A2 serves as a restriction element in NSCLC. More importantly, at least one **HER2** /neu-derived peptide is a tumor-associated antigen in NSCLC and ovarian cancer.

9/3,AB/12

DIALOG(R) File 155:MEDLINE(R)

08117836 94243246 PMID: 8186664

Oncogene overexpression in non-small-cell lung cancer tissue: prevalence and clinicopathological significance.

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Clinical investigator (GERMANY) Jan 1994, 72 (2) p156-63, ISSN 0941-0198 Journal Code: 9207154

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In contrast to small-cell lung cancer, few data are available on the role of oncogene overexpression in non-small-cell lung cancers (NSCLC). To determine the prevalence and extent of the transcriptional activation of cancer genes in NSCLC we investigated the level of mRNA of the three important cellular oncogenes-- **erbB2**, Ki-ras, and c-myc--in 39 surgically or endoscopically obtained tumor samples and 24 samples of normal bronchopulmonary tissue taken from the same patients. Tissue RNA was prepared and the specific mRNA analyzed by the highly sensitive nuclease S1 protection assay. Oncogene mRNA in the tumors was quantified by comparison with the homogeneously weak signals in normal lung tissue preparations with densitometry. The presence of two- to four-fold excess RNA was defined as moderate and a greater than fourfold RNA amount as strong gene overexpression. In contrast to normal tissue the oncogene mRNA amount varied considerably among tumors, showing increases up to 64-fold in **erbB2**, 13-fold in Ki-ras, and 57-fold in c-myc. Moderate and strong (in brackets) mRNA overexpression occurred with 33% (33%) in **erbB2**, 36% (18%) in Ki-ras, and 18% (23%) in c-myc. Simultaneous overexpression of two genes was observed with 41% and increased mRNA of all genes tested with 20% of the NSCLC samples. Augmented oncogene mRNA was observed most frequently in large-cell carcinoma. The c-myc overexpression was significantly more prevalent in large-cell cancer than in adenocarcinoma. Tumor differentiation was negatively correlated with c-myc mRNA amounts. (ABSTRACT TRUNCATED AT 250 WORDS)

9/3,AB/13

DIALOG(R) File 155:MEDLINE(R)

08096855 94219837 PMID: 8166465

The molecular and cellular basis of human lung cancer.

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Anticancer research (GREECE) Jan-Feb 1994, 14 (1B) p261-7, ISSN 0250-7005 Journal Code: 8102988

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Lung cancer arises after a series of morphological changes, which take several years to progress from normal epithelium to invasive cancer. The morphological changes progress from hyperplasia, to metaplasia, to dysplasia, to carcinoma in situ, to invasive cancer and finally to metastatic cancer. Multiple molecular changes have been documented in lung cancers, both small cell (SCLC) and non-small cell (NSCLC) types. The number of changes has been estimated to be in double digits. How can so many changes develop in one cell? One possible explanation is the "field cancerization" theory, that states that all or much of the aerodigestive tract epithelium has been mutagenized, perhaps as the result of exposure to tobacco products or other carcinogens. The molecular changes include activation of dominant oncogenes (myc family, K-ras and **HER / 2 / neu** genes), as well as loss of recessive growth regulatory genes or anti-oncogenes (p53, and rb as well as unidentified gene or genes on chromosome 3). However, cytogenetic and molecular genetic studies indicate that multiple other specific sites of actual or potential DNA loss may be present in lung cancers. Many of the well characterized molecular changes may function as negative prognostic factors for survival in subsets of lung cancers. Other changes may include development of drug resistance, and production of growth factors and their receptors. It is tempting to associate specific molecular changes with specific morphological changes, as has been attempted in the colon. However, because of the difficulties in serially sampling the respiratory tract, only a modest amount of data has been collected to date. It appears that deletions of chromosome 3p, hyperproliferation and aneuploidy are early changes, while p53 mutations appear later in the preneoplastic cascade. Documentation of intermediate

markers for lung cancer and prospective studies of their prognostic effects will be necessary for the design of rational chemoprevention trials.
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